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☐ 1: Neurochem Int. 1998 May-Jun;32(5-6):493-504.

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## Apoptosis by 2-chloro-2'-deoxy-adenosine and 2-chloro-adenosine in human peripheral blood mononuclear cells.

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Adenosine has profound effects on immune cells and has been implicated in the intrathymic apoptotic deletion of T-cells during development. In order to characterize adenosine effects on quiescent peripheral blood mononuclear cells (PBMC), we have evaluated the ability of the previously characterized adenosine receptor agonist 2-chloro-adenosine (2CA; Ceruti, Barbieri et al., 1997) and of the antineoplastic drug 2-chloro-2'-deoxy-adenosine (2CdA, cladribine) to trigger apoptosis of PBMC. Apoptosis was assessed by morphological changes, DNA fragmentation by agarose gel electrophoresis and appearance of hypodiploid DNA peak by flow cytometry. 2CA (10 microM) and 2CdA (1 microM) induced apoptosis in human PBMC, which are relatively insensitive to apoptosis. For both agents, the effect was concentration- and time-dependent, although 2CdA induced apoptosis more potently than 2CA. Evaluation of mitochondrial function in parallel samples using the mitochondrial membrane-potential-specific dye JC-1 showed that mitochondrial damage followed the same kinetics as apoptosis, hence an early damage of mitochondria is likely not responsible for adenosine-induced death of PBMC. The effect of 2CA was partially prevented by addition of dipyridamole (DP), a nucleoside transport inhibitor, hence some of the apoptotic effect of this nucleoside is, at least in part, due to intracellular action. Alternatively, DP did not affect 2CdA-induced apoptosis, suggesting that 2CdA may enter cells via a DP-insensitive transporter. 5-Iodotubercidin (5-Itu), a nucleoside kinase inhibitor, was also able to partially prevent the action of 2CA and was not able to affect 2CdA-induced apoptosis, suggesting a different role for phosphorylation in 2CA- vs 2CdA-induced apoptosis. To test the role of P1 receptors, agonists and antagonists selective at various P1 receptor subtypes were used. Data suggest that, for 2CA, apoptosis is partially sustained by activation of the A2A receptor subtype, whereas no role is exerted by P1 receptors in 2CdA-dependent apoptosis. Moreover, in these cells, apoptosis could also be triggered through intense activation of the A3 receptor via selective agonists such

as 2-chloro-N6-(3-iodobenzyl)adenosine-5'-N-methyluronamide (Cl-IB-MECA), but this mechanism plays no role in either 2CA- or 2CdA-induced apoptosis. On the whole, our results suggest that 2CA and 2CdA follow different pathways in inducing apoptosis of immune cells. Moreover, our data also suggest that there are at least three different ways by which adenosine derivatives may induce apoptosis of human PBMC: (i) through an A2A-like extracellular membrane receptor; (ii) through entry of nucleosides into cells and direct activation of intracellular events involved in the apoptotic process; or (iii) through activation of the A3 receptor.

PMID: 9676749 [PubMed - indexed for MEDLINE]

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